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PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :
A61K 9/40, 9/14, 9/22
A61K 9/26, 9/32

A1

(11) International Publication Number: WO 92/10173

(43) International Publication Date: 25 June 1992 (25.06.92)

(21) International Application Number: PCT/US91/09221

(22) International Filing Date: 4 December 1991 (04.12.91)

(30) Priority data:
622,875 5 December 1990 (05.12.90) US

(60) Parent Application or Grant
(63) Related by. Continuation
US 622,875 (CIP)
Filed on 5 December 1990 (05.12.90)

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(81) Designated States: AT (European patent), AU, BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, KR, LU (European patent), MC (European patent), NL (European patent), SE (European patent), US.

Published
With international search report.

(54) Title: PHARMACEUTICAL COMPOSITIONS

(57) Abstract

The present invention provides for a phased-release oral dosage form comprising a plurality of H_2 receptor antagonist pellets in a polymer matrix. Each phase, containing a plurality of pellets which may be optionally coated with a release delaying substance, may have different release rates, thereby providing release of the H_2 antagonist over an extended duration of time.

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PHARMACEUTICAL COMPOSITIONS

FIELD OF THE INVENTION

This invention relates to solid oral pharmaceutical compositions containing cimetidine.

BACKGROUND OF THE INVENTION

Cimetidine is a histamine H_2-antagonist which has been described in U.K. Patent Specification 1,397,436. Cimetidine has been shown to be useful in the treatment of duodenal, gastric, recurrent and stomal ulceration, and reflux oesophagitis and in the management of patients who are at high risk from haemorrhage of the upper gastrointestinal tract.

Cimetidine has been made available to patients in a variety of dosage forms; for example, tablets, granules, syrups and suspensions. In most, if not all, of these dosage forms, the cimetidine is in an immediate-release form; that is to say the nature of the formulation is such that by the time the cimetidine leaves the stomach, it is either in solution or is in the form of a suspension of fine particles, i.e. a form from which it can be readily absorbed.

Coating agents which prevent release of an active ingredient in the stomach but which allow release in the intestines are known as enteric coating agents and many such substances are known in the art for this purpose. Similarly, agents which form a matrix in which the active ingredient is embedded are known to modify the release of the active ingredient. However, it has been found that, when many such release delaying substances are used in conjunction with cimetidine, although release is delayed, the bioavailability of the cimetidine is substantially reduced.

SUMMARY OF THE INVENTION

The present invention provides for a phased-release oral dosage form comprising an H_2 antagonist in a polymer matrix. The dosage form may comprise a plurality of matrix cores containing an H_2 antagonist which matrix cores have different release rates or modified-release phases as used herein. The phased-release (or modified-release phase) may contain two, three, four or more phases of modified-release polymer matrix-cores (or matrixes). The dosage form preferably comprises an immediate-release

phase of cimetidine as well as the modified release phase. The modified release phase alone or in combination with immediate release of cimetidine is able to extend the duration of action of cimetidine and thereby provide improved bioavailability of cimetidine.

DETAILED DESCRIPTION OF THE INVENTION

In one aspect, the present invention is a modified-release dosage form which comprises an H_2 antagonist in a polymer matrix core. The modified release form, preferably composed of pellets, comprises a plurality of discrete polymer matrix particules suitable for combination into an oral dosage form. The oral dosage form may comprise multiple release phases of matrixes each of which comprises an H_2 antagonist incorporated, independently, into the polymer matrixes.

The modified release phase matrix-core may be un-coated (hereinafter referred to as the "uncoated matrix") or coated (hereinafter referred to as a "coated matrix") with a release-delaying substance. Preferably, when the matrix-core is coated with the release delaying substance, the release delaying substance is present in an amount of from 2 to 30% (w/w) relative to the matrix-core. More preferably, the release-delaying substance is present in an amount of from 5 to 25% (w/w).

Another aspect of the present invention provides for various combinations of modified-phase release pellets with other pellets, for example, the uncoated matrix pellets may be in combination with 1) an immediate release phase pellet of the same H_2 antagonist, preferably cimetidine; 2) a coated matrix pellets containing the same H_2 antagonist; 3) coated matrix pellets with immediate release phase pellets; 4) coated matrix pellets in combination with additional uncoated matrix pellets of a different polymer base; 5) coated matrix pellets in combination with additional uncoated matrix pellets of a different polymer base and immediate release phase pellets. The matrix-core pellets may be coated independently with different release-delaying substances all of which may be combined with the uncoated or immediate release phase pellets of cimetidine. Therefore, additional combinations such as changing the polymer bases for the coated and uncoated matrixes as well as changing the release delaying substance in each of the above noted combinations is also contemplated within the scope of the invention.

Yet another aspect of the present invention provides for an additional modified-release phase to be present in combination with the coated or un-coated matrix, with or without immediate release, which additional modified-release phase comprises at least one core of cimetidine coated with a release-delaying substance (hereinafter referred to as "immediate coated"). The release-delaying substance present in the immediate coated pellets is present in an amount from about 2 to about 30% (w/w) relative to the granule. Preferably the substance is present in an amount of 5 to 25% (w/w).

More preferably this invention provides for combinations of the immediate coated pellets with coated matrix and immediate release pellets; as well as various combinations of immediate coated pellets with uncoated matrix and immediate release pellets; as well as immediate coated pellets with coated matrix and un-coated matrix pellets. The combination of all four types of pellets (immediate-release, immediate coated, un-coated matrix and coated matrix) is also contemplated as a further aspect of the present invention and is described below in its preferred embodiment :

A modified-release oral dosage form comprising:

a) an immediate-release phase of cimetidine;

b) a "first" modified release phase which comprises a matrix-core which comprises cimetidine incorporated into a polymer matrix;

c) a "second" modified release phase matrix-core which comprises cimetidine incorporated into a polymer matrix coated with a first modified release-delaying substance in an amount of from 2 to 30% (w/w) relative to the matrix-core (hereinafter referred to as a "coated matrix"); and

d) a "third" modified-release phase which comprises at least one core of cimetidine coated with a second modified release-delaying substance in an amount of from 2 to 30% (w/w) relative to the core (hereinafter referred to as "immediate coated").

As the release-delaying substances, which can for instance be enteric coatings, slow release, or delayed release, may vary independently with the matrix core(s) or the immediate release pellets of cimetidine, therefore all combinations of such coatings are contemplated to be within the scope of this invention. Further, as the polymer used to granulate the matrix can vary with the release phase desired, the various combinations of matrixes having different polymer cores is also contemplated within the scope of this invention.

Examples of H_2 antagonists useful in the present invention include, but are not limited to, cimetidine, rantidine, famotidine, nizatidine and roxatidine.

Immediate release phase, as used herein, is intended to mean a short pulse, i.e., a dissolution time and absorption from the gastric juices from immediate release to about 45 minutes. The immediate-release phase of the present invention contributes to a first pulse of cimetidine in the stomach. Such immediate-release formulations for instance of cimetidine are old and well known to those skilled in the art, for example, U.S. Patent No. 4,024,271 issued May 17, 1977. The immediate release phase pellets of the present invention, as described in the Example Section, herein meet such criteria. The immediate

release phase of the present invention preferably comprises cimetidine as a pellet or granule (one core) not comprising a delayed released substance.

Modified release phase, as used herein, is intended to mean a controlled release of cimetidine such that cimetidine is not immediately and completely released into the stomach, within the time frame noted above, and remains available to the mammal for release over a prolonged period of time. The release may occur in the stomach or the intestinal tract.

The immediate coated release pellets of the present invention, are made from coated "immediate release" pellets of cimetidine. However, it is within the scope of this invention that any immediate release form of cimetidine is contemplated and is not limited to a bead or pellet formulation as described herein. Bulk cimetidine, granulated cimetidine and coated cimetidine particles thereof are but one aspect of the present invention. The overcoating as contemplated herein for the immediate release dosage forms, are the enteric coatings. The enteric coating art is well known to those skilled in the art and is suitably described in Example 1 herein. The immediate coated release pellets of the present invention will allow for release of the cimetidine over a period of time in the intestinal tract (dependent upon the type and amount of coating chosen).

The "release delaying substance" of the present invention, as used herein, is a coating agent or blend of agents thereof, which protects the active ingredient, the H_2 antagonist, from immediate degradation in the stomach. The overcoating, depending upon the release rate desired may allow for continual release (or slow release) or may be a delayed release.

The modified release phase of an uncoated matrix pellet, as used herein, will result in a pulse of cimetidine which, depending upon the polymer used in the matrix itself, continue to release cimetidine for a period of time exceeding that of the immediate release. Preferably the release will continue for up to 4 hours. More preferably the release will continue for up to 8 hours. A preferred embodiment of the invention is an immediate release of the H_2 antagonist, followed by a 10% release of the H_2 antagonist by 4 hours, followed thereby with a 10 to 15% release rate each hour up to 8 hours.

The modified release phase of a coated matrix pellet as used herein, results in the absence of available cimetidine in the stomach and allows for its release in the intestinal tract , i.e. as a "third" pulse in combination with immediate and uncoated matrix pellets. Dependent upon the coating and polymer used in the matrix a prolonged release of cimetidine in the intestinal tract will occur over an extended period of time. In this manner the duration of action of cimetidine can be extended providing good bioavailability.

Extending the duration of action of cimetidine increases the rate of healing in gastric or duodenal ulceration and is advantageous in disease states such as gastro-esophageal reflux disease, dyspepsia or stress ulceration where prolonged control of acid secretion is desirable.

The cimetidine may be present as the free base or as a pharmaceutically acceptable salt, for example the hydrochloride salt.

The immediate-release phase of cimetidine can exist in any of the commonly used types of solid dosage form, for example, as tablets, pellets or granules which can optionally be coated with a coating agent which dissolves in the gastric juices or which can optionally be contained within a gelatin capsule.

The modified release phase matrix can similarly exist as a tablet, pellet or granule and is optionally coated with the release-delaying substance. The additional modified-release phases, such as the immediate coated may also exist as a tablet, pellet or granule coated with the same, or different release-delaying substance, and which can optionally be contained within a gelatin capsule..

The immediate and modified-release phases can be presented separately or more conveniently combined in a single dosage form. Thus, for example, a combination can take the form of immediate-release phase pellets, "first modified-release phase" un-coated matrix pellets, "second modified-release phase" coated matrix pellets, and "third modified-release phase" immediate coated pellets, all optionally contained within a gelatin capsule. It is possible to have various combinations of the dosage forms, such as immediate release with coated matrix; immediate release with uncoated matrix; immediate release with immediate coated and coated matrix; or immediate release with immediate coated and un-coated matrix.

The immediate release phase and the modified release phase (an uncoated matrix, coated matrix or immediate coated pellet) are preferably contained in a single dosage form. The immediate release phase and modified release phase are preferably composed of pellets or beads (used interchangeably herein). The pellets are preferably contained in a capsule, which is preferably made of gelatin.

For particulate dosage forms such as pellets or granules and in a two phase system, of the total amount, preferably the immediate release phase is present in an amount of about 5 to 40% (w/w). The first and second modified release substance (the coated or un-coated matrix respectively) is thereby present in an amount of 60 to 95% (w/w) relative to the immediate release dosage form. Preferably, either matrix is present in an amount of 70 to 90% (w/w) relative to the immediate release form of 10 to 30% (w/w).

For a three phase system, which can include either or both of the coated and un-coated matrixes, of the total amount, the immediate release dosage form is present in an amount of about 5 to 40%, the coated matrix dosage form is present in an amount of about 10 to 85% (w/w) relative to the immediate release dosage and an immediate coated dosage form is present in an amount of about 10 to 85% (w/w) also relative to the immediate release dosage form.

Preferably the immediate release dosage form is present in an amount of about 5 to 30%, the coated matrix dosage form is present in an amount of about 20 to 75% (w/w), and the immediate coated dosage form is present in an amount of about 20 to 75% (w/w). The modified release substances should preferably be present in about 66 to 75% total (w/w) of the cimetidine dosage form. More preferably the immediate release dosage form in present in an amount of about 15 to 25%, the immediate enteric coated dosage form is present in an amount of about 20 to 30%, and the coated matrix dosage form is present in an amount of 45 to 60%.

For the four phase system, the immediate release dosage form is present in an amount of about 5 to 40%, the (un)-coated matrix dosage form is present in an amount of about 10 to 75% (w/w) relative to the immediate release dosage and the immediate coated dosage form is present in an amount of about 5 to 75% (w/w) also relative to the immediate release dosage form.

Preferably the immediate release is present in an amount of about 5 to 30%, the coated matrix in an amount about 20 to 70% (w/w), the un-coated matrix in an amount about 20 to 70% (w/w), and the immediate coated substance in present in an amount about 10 to 30% (w/w). As in the case of the three phase system, the modified release substances should preferably be present in about 66 to 75% total (w/w) of the total dosage form.

Suitably the coating agents used for the immediate-release phase of cimetidine will dissolve in the gastric juices. Such coating agents are well known to those skilled in the art and include, but are not limited to hydroxypropyl methylcellulose, or methyl cellulose.

Suitably the coating agents used for the modified-release phase matrixes are agents or blends of agents such as, but not limited to, enteric coating agents selected from copolymers based on methacyrlic acid and ethyl acrylate; copolymers based on methacyrlic acid and methacrylates (also referred to as methacrylic acid copolymers, Type A-C United States Pharmacopia, 22nd Edition); copolymers based on hydroxypropyl methylcellulose phthalate, cellulose acetate phthalate, polyvinyl acetate phthalate, or mixtures thereof. The coating agents of the additional, or second and third

modified-release phase substances need not be the same, however, conveniently they are essentially the same.

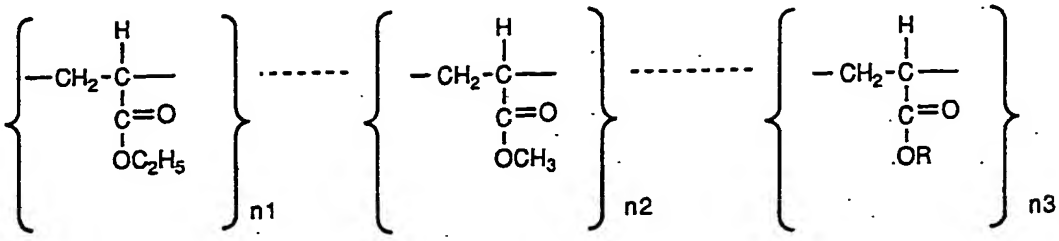
Preferably the coating agent is Eudragit ™L30D which is an aqueous dispersion containing 30% (w/w) of an acrylic resin formed from a copolymer based on polymethacrylic acid and acrylic acid esters. The acrylic resin is soluble in intestinal juice from pH 5.5 upwards.

The process of producing the coated modified-release phase tablets, pellets and particules is also well known to those skilled in the art and may be readily achieved by suspending the material to be coated in fluidized bed equipment, spraying the coating solution onto the material and subsequently drying. Alternatively, the coating can be carried out in pans designed for such purpose and employing similar spraying techniques to coat materials and subsequently drying thereafter.

The matrix material comprising the modified release phase contains a suitable polymer which forms a matrix from which the cimetidine can be gradually released. Suitable materials are the water swellable polymers, or polymers which are non-water swellable but water permeable. Examples of suitable polymers useful in this invention include, but are not limited to a non-ionic neutral copolymers based on ethyl acrylate and methyl acrylate (also referred to as polyacrylates), such as Eudragit™ NE30D, acrylic and methacrylic acid esters, such as Eudragit™ RS30D, ethyl cellulose, hydroxypropyl methylcellulose, gelatin or various waxes (such as, but not limited to, white, carnauba, stearyl alcohol, stearic acid, polyethylene glycol, castor wax, polyethylene glycol monostearate and triglycerides) or mixtures thereof.

A preferred polymer is Eudragit™ NE 30D which is an aqueous dispersion containing 30% (w/w) of a neutral copolymer based on ethyl acrylate and methyl acrylate, and is considered a water swellable and water permeable polymer. Another preferred polymer are the co-polymers of acrylic and methacrylic acid esters (Eudragit™ RS 30D), which is not water swellable and has a low permeability to water. Another preferred polymer similar to Eudragit ™RS 30D is one based upon the same structure but which has additional ammonium groups, such as Eudragit™ RL 30D. This copolymer is not water swellable but is very permeable to water. Both Eudragit™ RS 30 D and RL 30 D are independent of pH.

A short chemical description of the preferred polymers, such as Eudragit™ RS 30D, RL 30D and NE 30D, produced by Rohm Pharma GMBH, Weiterstadt is shown below.



Polymer Name	$n_1:n_2:n_3$	M.W.	Eudragit type	
Poly(ethylacrylate, methylmethacrylate)	2: 1	800,000	NE 30D	
Poly(ethylacrylate, methylmethacrylate) trimethyl-ammonioethylmethacrylate chloride $R = CH_2\text{-}CH_2\text{-}N^+(CH_3)_3Cl^-$	1: 2: 0.2	150,000	RL 30D RL 100	(30% dispersion) (granules)
Poly(ethylacrylate, methylmethacrylate) trimethyl-ammonioethylmethacrylate chloride $R = CH_2\text{-}CH_2\text{-}N^+(CH_3)_3Cl^-$	1: 2: 0.1	150,000	RS 30D RS 100	(30% dispersion) (granules)

A preferred usage of these copolymers in the instant invention is to mix Eudragit™ RS 30D and Eudragit™ RL 30D in ratios from 0 to 100% w/w to produce the desired release profile. A preferred ratio of RS 30D to RL 30D (for matrix use) is from 95:5 to 60:40. Another preferred combination is to mix Eudragit™ RS 30D and Eudragit™ NE 30D in ratios of 0 to 100% w/w as well. The preferred ratios of Eudragit™ RS 30D to NE30D (for matrix use) are from 95:5 to 50:50, more preferably 85:15. The polymers can be used alone, or in combination to produce a delayed (or controlled) release of the H_2 antagonist either by incorporation into the matrix granulation and optionally with overcoating the matrix cores by the copolymers. For instance, if Eudragit™ NE 30D is the copolymer used for the matrix granulation core then Eudragit™ RS 30D may be used as the copolymer for over-coating. Alternatively, Eudragit™ RS 30D could be used for the matrix granulation core material and the overcoating copolymer may be Eudragit™ NE 30D.

Preferably the matrix granulation polymer is present in an amount of 10 to 20% (w/w) of polymer relative to the H_2 antagonist or cimetidine (based upon dry weight of polymer).

The matrix granulation core w/w % is dependent upon the concentration of the polymer suspension. For instance, the preferred polymer Eudragit™ NE 30D is available as aqueous dispersion containing 30% (w/w) of the neutral copolymer as well as a 40% and a 50% concentration. As cimetidine is fairly soluble in water, the amount of suspension which can be used is restricted as the granulation becomes overwet. If a more concentrated suspension is used a higher level of polymer may be obtained in the matrix bead. If more polymer is used there will be a decrease in the amount of cimetidine available. Yet another factor for ultimately determining the correct percentage of polymer used in the matrix granulation is the amount of retardant or release-delaying substance applied. An increase of release-delaying substance would decrease the amount of polymer used in the matrix granulation.

A preferred embodiment of the present invention is a matrix granulation core containing 12% w/w of polymer. If the matrix core is coated with a release-delaying substance of the type which causes a slow release (as opposed to a delayed release), the preferred percentage of polymer used will be from about 2 to about 30%, preferably from about 2 to about 20%. A slow release overcoating w/w % would preferably be from about 2 to about 20% as well. More preferably about 10%.

A further preferred embodiment of the present invention is a matrix granulation core which is overcoated with a retardant (or delayed release) polymer. Similar preferred ratios of polymers are those noted above.

The formulations of the present invention may further comprise additional excipients and agents well known in the coating art such as:

1) plasticisers, e.g. acetylated monoglycerides, diethyl phthalate, triacetin, citric esters such as triethyl citrate, acetyl triethyl citrate, tributyl-citrate or acetyl tributyl citrate, propylene glycol, tributyrine, butylphthalylbutyl glycolate, glycerine, polyethylene glycols, glyceryl triacetate, dibutyl sebacate, dibutyl phthalate, castor oil or acetyl monoglyceride, polysorbates and sodium lauryl sulfate;

2) lubricants, e.g. calcium stearate, colloidal silicon dioxide, mineral oil, magnesium stearate, polyethylene glycol or talc; or

3) film disintegrating agents, e.g. lactose, saccharose, starch, cellulose, kaolin, polyvinyl alcohol or hydroxypropyl methyl cellulose.

The immediate-release and modified-release phases forms of this invention suitably comprise other standard pharmaceutically acceptable carriers or excipients, for example starch, celluloses, sodium croscarmellose, sodium starch glycoate, crospovidone, polyvinyl alcohol, polyvinylpyrrolidione, gelatin, low viscosity

hydroxypropyl methylcellulose, lactose, sucrose, talc, kaolin, colloidal silicon dioxide, magnesium stearate, or stearic acid.

The process of producing immediate release substance is well known to those skilled in the art. For instance the H_2 antagonist can be granulated in accordance with standard pharmaceutical techniques; thus is can be mixed with a solution of a binding agent in a conventional mixing device or it can be subjected to fluidized bed granulation methods as known in the art. The process of producing the modified release phase is also well known to those skilled in the art and is further illustrated by means of the following examples.

EXAMPLE 1

Uncoated immediate-release cimetidine pellets, un-coated matrix pellets, and immediate coated pellets are contained within a hard gelatin capsule.

Manufacture of Immediate-Release Pellets

Ingredients	% w/w
Cimetidine	85
Microcrystalline Cellulose	12
Gelatin	3
Water	(qs)

The cimetidine and part of the microcrystalline cellulose are dry blended in a high shear mixer. Mixing is continued while a solution of the gelatin in water is added. When homogeneously massed the material is passed through an extruder and recirculated through it once. The extrudate is transferred to a Marumerizer bowl and spheronized. The rest of the microcrystalline cellulose is used as dusting powder to facilitate this stage of the process. The pellets are discharged and spread out on trays to be dried in a hot air oven. The dried pellets are screened via a 1.4mm sieve to remove oversize and via a 0.6mm sieve to remove undersized fractions. Pellets fractions between 600 microns and 1400 microns in diameter are retained. These dried uncoated immediate-release pellets therefore contain 85% of cimetidine.

Coating of Immediate-Release Pellets to yield Immediate Coated Pellets

Composition of coating suspension % w/w

Eudragit ™L30D	51.2
Triethyl citrate	2.3
Colloidal silicon dioxide	1.2
Water	45.3

Pellets obtained as described above are coated by bottom spraying with the coating suspension in Fluidized Bed equipment until a 20% gain in weight is achieved. These coated pellets therefore contain 85/120 = 70.8% of cimetidine. The coated pellets are dried in situ before discharge, and then allowed to cure overnight at room temperature, while spread out on trays. The approximate weight of a coated pellet is about 0.8 mg.

Manufacture of Cimetidine Polymer Matrix-Pellets

(Uncoated Matrix Pellets)

Ingredients of Core	% w/w
Cimetidine	75
Microcrystalline Cellulose	10
Gelatin	3
Eudragit NE 30 D	12*
Water	(qs)

* Calculated as dry weight of polymer

The cimetidine polymer matrix-pellets are prepared in similar manner to the immediate-release pellets except that the Eudragit ™NE 30 D suspension is added prior to the addition of the gelatin solution. Dried uncoated cimetidine polymeric matrix-pellets therefore contain 75% of cimetidine.

Encapsulation

The coated and uncoated pellets are prepared as in Example 1 are filled (encapsulated) into capsules, such that one capsule contains:

58.8 mg of uncoated immediate release pellets comprising 50 mg cimetidine;

70.6 mg of immediate coated pellets comprising 50mg cimetidine; and

266.7 mg of coated matrix pellets comprising 200 mg cimetidine.

Thus two capsules provides a 600mg dose of cimetidine.

EXAMPLE 2

Immediate-release cimetidine pellets, and uncoated matrix are contained within a hard gelatin capsule.

Manufacture:

The un-coated matrix pellets and immediate release cimetidine pellets are prepared as in Example 1.

Encapsulation:

These pellets are filled (encapsulated) into capsules, such that one capsule contains:

88.2mg of uncoated immediate release pellets comprising 75mg cimetidine, and 300mg of uncoated matrix pellets comprising 225mg cimetidine.

When prepared in accordance with these procedures, one capsule would provide a 300mg dose of cimetidine.

Alternatively, the pellets may also be encapsulated such that one capsule contains :

58.8 mg of uncoated immediate release pellets comprising 50mg cimetidine, and 333.3 mg of uncoated matrix pellets comprising 250mg cimetidine.

EXAMPLE 3

Uncoated immediate-release cimetidine pellets, coated matrix pellets, and immediate coated pellets are contained within a hard gelatin capsule.

The immediate coated cimetidine pellets and immediate release pellets are prepared as in Example 1, above.

Coating of the Uncoated Polymer Matrix Pellets

(Coated Matrix Pellets)

The uncoated matrix cimetidine pellet is first prepared using the procedures described above in Example 1 for preparation of the un-coated Cimetidine Polymer Matrix pellets. The uncoated pellet is then coated in an analogous manner and with the same coating suspension as described in Example 1 for the immediate coated pellets. When prepared in accordance with these procedures the coated pellets contain 75/120 = 62.5% of cimetidine.

Encapsulation

The coated and uncoated pellets as prepared above are filled (encapsulated) into capsules, such that one capsule contains:

58.8 mg of uncoated immediate release pellets comprising 50 mg cimetidine;

141.2 mg of immediate coated pellets comprising 100mg cimetidine; and

240.0 mg of coated matrix pellets comprising 150 mg cimetidine.

Thus two capsules provides a 600mg dose of cimetidine wherein the ratio of immediate release, immediate coated and coated matrix is 1:2:3 [50+100+150 = 300mg].

EXAMPLE 4

Uncoated immediate-release cimetidine pellets, and coated matrix pellets are contained within a hard gelatin capsule.

The immediate release pellets are prepared as described above, in Example 1. The coated matrix pellets are prepared as described in Example 3. These pellets are filled (encapsulated) into capsules, such that one capsule contains:

117.6mg of uncoated immediate release pellets comprising 100mg cimetidine, and

320mg of coated matrix pellets comprising 200mg cimetidine.

Alternatively, the pellets may be encapsulated such that one capsule contains:

88.2 mg of uncoated pellets comprising 75mg cimetidine, and

360.0 mg of coated matrix pellets comprising 225mg cimetidine.

EXAMPLE 5

Uncoated immediate-release cimetidine pellets, uncoated matrix pellets, coated matrix pellets, and immediate coated pellets are contained within a hard gelatin capsule.

Manufacture:

The uncoated matrix is prepared as described above in Example 1. The coated matrix is prepared, as described above, in Example 3. The immediate release and immediate coated release pellets are also prepared, as described above, in Example 1.

Encapsulation

Uncoated and coated pellets are filled into capsules such that one capsule contains :

29.4 mg of uncoated pellets comprising 25 mg cimetidine (8.3%)

35.3 mg of coated pellets (immediate-coated) comprising 25 mg cimetidine (8.3%)

133.3 mg of uncoated polymer matrix-pellets comprising 100 mg cimetidine (33.3%)

240.0 mg of coated polymer matrix-pellets comprising 150 mg cimetidine (50%).

EXAMPLE 6

For systems consisting of coated matrix beads the following combinations are exemplified. The amount of coating present is expressed as a % weight gain over the granule alone.

MATRIX CORE	(amount of polymer w/w)	COATING	
Eudragit™ NE 30D	12%	none	
NE 30 D	12%	Eudragit™ L 30D	10% Wt. gain
NE 30 D	12%	NE 30D	10% Wt. gain
NE 30 D	12%	RS 30D	10% Wt. gain

MATRIX CORE	(amount of polymer w/w)	COATING	
RS:RL 30D	(90:10 ratio, 20%)	none	10 % Wt. gain
RS:RL 30D	(90:10, 20%)	Eudragit™ L 30D	10 % Wt. gain
RS:RL 30D	(90:10, 20%)	NE 30D	10 % Wt. gain
RS:RL 30D	(90:10, 20%)	RS 30D	10 % Wt. gain
RS:NE 30D	(85:15 ratio, 15%)	none	10 % Wt. gain
RS:NE 30D	(85:15, 15%)	Eudragit™ L 30D	10 % Wt. gain
ATRS:NE 30D	(85:15, 15%)	NE 30D	10 % Wt. gain
RS:NE 30D	(85:15, 15%)	RS 30D	10 % Wt. gain

The above description fully discloses the invention including preferred embodiments thereof. Modifications and improvements of the embodiments specifically disclosed herein are within the scope of the following claims. Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. Therefore the Examples herein are to be construed as merely illustrative and not a limitation of the scope of the present invention in

any way. The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows.

What is claimed is :

1. A phased-release oral dosage form comprising an H_2 antagonist in a polymer matrix.

2. The dosage form according to Claim 1 wherein the H_2 antagonist is cimetidine.

3. The dosage form according to Claim 2 which comprises a plurality of polymer matrix cores.

4. The dosage form according to Claim 3 wherein the polymer matrix is selected from the group consisting of a non-ionic neutral copolymer of ethyl acrylate and methyl acrylate, acrylic and methacrylic acid esters, ethyl cellulose, hydroxypropyl methylcellulose, gelatin, waxes or mixtures thereof.

5. The dosage form according to Claim 4 wherein the polymer matrix is a copolymer of ethyl acrylate and methyl acrylate.

6. The dosage form according to Claim 4 wherein the polymer matrix is a co-polymer of acrylic and methacrylic acid esters.

7. The dosage form according to Claim 4 wherein the polymer matrix is a co-polymer of Eudragit™RL 30D.

8. The dosage form according to Claim 4 wherein the polymer matrix material is present in an amount of 10 to 20% (w/w) of polymer relative to cimetidine.

9. The dosage form according to Claim 4 wherein the dosage form is composed of pellets.

10. The dosage form according to Claim 9 wherein the pellets are contained in a gelatin capsule.

11. The dosage form according to Claim 4 wherein at least one of the matrixes is independently coated with a release-delaying substance.

12. The dosage form according to Claim 11 wherein the release-delaying substance is a coating agent selected from the group consisting of co-polymers based on polymethacrylic acid and methacrylates, ethyl acrylate and methyl acrylate, co-polymers of acrylic and methacrylic acid esters, co-polymers of Eudragit™RL 30D, hydroxypropyl methylcellulose phthlate, cellulose acetate phthalate, polyvinyl acetate pthtalate or mixtures thereof.

13. The dosage form according to Claim 12 wherein the coating agent is a copolymer of polymethacrylic acid and methacrylates, methacrylic acid and ethylacrylate, or co-polymers of Eudragit™RL 30D.

14. The dosage form according to Claim 13 wherein the release-delaying substance is present in an amount of from 2 to 30% (w/w) relative to the matrix-core.

15. The dosage form according to Claim 1 or 3 which further comprises an immediate release phase.

16. The dosage form according to Claim 14 wherein the phased-release phase is present in an amount of 66 to 75% (w/w) relative to the immediate release phase.

17. The dosage form according to Claim 16 wherein the matrix core is optionally coated with a release-delaying substance.

18. The dosage form according to Claim 17 wherein the immediate release phase is optionally coated.

19. A modified-release oral dosage form comprising:

a) an immediate-release phase of cimetidine;

b) a modified-release phase which comprises cimetidine incorporated into a polymer matrix;

c) a second modified-release phase which comprises cimetidine incorporated into a polymer matrix coated with a release-delaying substance in an amount of from 2 to 30% (w/w) relative to the matrix-core;

d) a third modified-release phase which comprises cimetidine coated with a release-delaying substance in an amount of from 2 to 30% (w/w) relative to the core.

20. The dosage form according to Claim 19 wherein the modified release phase is present in an amount of 66 to 75% (w/w) relative to the immediate release phase.

21. The dosage form according to Claim 20 wherein the polymer matrix material is present in an amount of 10 to 20% (w/w) of polymer relative to cimetidine.

22. A phased-release oral dosage form comprising:

a) an immediate-release phase of cimetidine;

b) an immediate coated release phase of cimetidine;

c) a modified-release phase which comprises cimetidine incorporated into a polymer matrix optionally coated with a release-delaying substance in an amount of from 2 to 30% (w/w) relative to the matrix-core.

23. A process for producing a phased release oral dosage form which process comprises granulating an H_2 receptor antagonist in a polymer matrix.

24. The process according to Claim 24 wherein the H_2 antagonist is cimetidine.

25. The process according to Claim 24 which comprises a plurality of polymer matrix cores.

26. The process according to Claim 25 wherein the polymer matrix is selected from the group consisting of a non-ionic neutral copolymer of ethyl acrylate and methyl acrylate, acrylic and methacrylic acid esters, ethyl cellulose, hydroxypropyl methylcellulose, gelatin, waxes or mixtures thereof.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US91/09221

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC (5): A61K 9/40, 9/14, 9/22, 9/26, 9/32
U.S. CL. 424/456

II FIELDS SEARCHED

Minimum Documentation Searched [7]

Classification System	Classification Symbols
U.S.	424/456, 484, 485, 486, 487, 488, 489

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
X	US, A, 4,940,588 (SPARKS ET AL) 10 JULY 1990 See column 5, line 31 and claim 2; column 7, lines 35-67 and column 8, lines 1-26.	1-26

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search

MARCH 02, 1992

Date of Mailing of this International Search Report

19 MAR 1992

International Searching Authority

ISA/US

Signature of Authorized Officer

Thurman K. Page

Thurman K. Page

GIV
80 Summit View Lane
Bastian, VA 24314
Telephone: 800-442-5198
Fax: 276-688-2504
E-mail: dbailey@giv.com

To: Kim Gearhart

From: Duane Bailey

Date: 5/22/2006

Pages: 2

Please process and confirm the attached order. If you have any questions, please let us know. Thanks and have a good day.

General Injectables & Vaccines, Inc.
80 Summit View Lane

P.O. Box 9
Bastian, VA 24314
1-276-688-4121

PURCHASE ORDER

Purchase Order No.	Revision	Page
74708	0	1

This Purchase Order Number MUST appear on all related correspondence, including invoices and packing slips.

Ship to
GIV
80 SUMMIT VIEW LANE
PO BOX 9
BASTIAN,VA 24314
United States

Bill to
80 SUMMIT VIEW LANE
PO BOX 9
BASTIAN ,VA 24314
United States

SANDOZ
PO BOX 65011
CHARLOTTE, NC 28265

Customer Account No.	Vendor No.	Date of Order/Buyer	Revised Date/Buyer
177528	8757	22-MAY-06 BAILEY, D	

Payment Terms	Ship Via	F.O.B.
2% 30 Days	BEST WAY	

Freight Terms	Request or Deliver to	Supplier Telephone
		(800) 523-1808

	Description/Item Number	Delivery Date	Quantity	Cost	Extended Amount	
1	340295 Your #: 00781-3402-95 AMPICILLIN SODIUM 250mg/vl PK/10 SANDOZ PDI o SHIP TO: Address at top of page	30-MAY-06	8.00 Pack	33.48	267.84	N
2	340795 Your #: 00781-3407-95 AMPICILLIN SODIUM 500mg/vl 6ml PK/10 SANDOZ PDI o SHIP TO: Address at top of page	30-MAY-06	5.00 Pack	35.24	176.20	N

DEA Number:		TOTAL 444.04
PG0229321		
		Authorized Signature

Form PO 2.0, 04-22-03 bw

CLINT PHARMACEUTICALS, INC.
629 SHUTE LANE
OLD HICKORY, TN 37138
PHONE: (615) 882-0042 FAX: (615) 882-0916

PURCHASE ORDER NO. 9870

VENDOR NAME	ACCOUNT #	TELEPHONE #	CONTACT	DATE
Sandoz	200980	fax 720-887-3910	Cust SVC	5-22-06

PRODUCT CODE/NDC #	DESCRIPTION	STRENGHT/SIZE	QUANTITY ORDERED	PRICE	TOTAL	QUANTITY RECEIVED	REC'D BY
3105-60	Cefotaxime	2gm/5ml	1512	20.80	31,449.60		
3105-60							
3105-60							
7813202 7.95	ceftriaxone	500mg	12x10	37.05	444.60		
		Please confirm order we need ASAP					
CONFIRMATION OR REFERENCE #							END

SDS SELECT PHARMACY SERVICES, INC
17 MT. SNOW LANE, CORAM, NY 11727 PHONE 631-474-4077 FAX 631-474-4088
email- selectpharm@yahoo.com

RESEARCH INQUIRY

FROM: LORETTA FREIRE, RESEARCH DEPT. DATE 5-22-06

TO: Rivera (Sandoz) NUMBER OF PAGES 1

ATT: RETURNED GOODS/ CREDIT DEPT.

FAX # 720-887-3910 PHONE # 800-525-8747

WOULD YOU PLEASE BE KIND ENOUGH TO CHECK YOUR RECORDS TO SEE IF A CREDIT HAS BEEN ISSUED TO THE FOLLOWING PHARMACY WHO RETURNED OUTDATED PRODUCT

ON: 12-7-05 ~~(SEE ENCLOSED RETURN GOODS FORM)~~

PHARMACY ANJO Enterprises dba/ Codman Square Pharmacy DEBIT MEMO NUMBER RW12705

ADDRESS: 624 Washington St, Dorchester, MA 02124

WHOLESALER: Cardinal, Peabody, MA

ACCOUNT # 631662 DEA # BA5277000

ANY INFORMATION YOU CAN PROVIDE US WITH, ESPECIALLY THE AMOUNT OF CREDIT OR CHECK ISSUED WOULD BE GREATLY APPRECIATED. WE LOOK FORWARD TO HEARING FROM YOU.

( )PHARMACY WAS PAID ( )OTHER (SEE NOTE BELOW)

( ) SENT TO PHARMACY ( ) SENT TO WHOLESALER

CREDIT MEMO # _____ CHECK # _____ AMOUNT $ _____

- REMARKS _____

PREPARED BY : _____ DATE : _____

Hemophilia of the Sunshine State

A Priority Healthcare Pharmacy

Joint Commission on Accreditation of Healthcare Organizations

TO: Sandoz
Phone 800-525-8747
Fax 720-887-3910

FROM: Hemophilia of the Sunshine State / ESI
Account No. 206117
Phone No. 800-684-2966
Fax No 813-854-1240

DATE: May 22, 2006
Purchase Order No. 052206BB

ORDER:

Ribavirin	200mg cap/84	00781-2043-04 Quantity 15
Ribavirin	200mg cap/56	00781-2043-16 Quantity 0
Ribavirin	200mg cap/70	00781-2043-67 Quantity 0

Please ship to: 4035 Tampa Road, Suite 6500, Oldsmar, FL 34677
Please ship: Second Day Air

Please confirm receipt of this order & ship date @ 800-684-2966

If you have any questions, please call @ 800-684-2966

Thank You

Bobbi Brown
4035 Tampa Road Suite 6500 Oldsmar, FL 34677 Pharmacy Phone 800 684-2966 Office Phone 813 854-1448
Pharmacy Fax 813 854-1240 Office Fax 813 855-6972
www.hemophilia.com

Chloe' Ross
Phone: 800-599-9894 x 5013
Fax: 800-599-9893
Chloe.Ross@mckesson.com

McKesson

Fax

To: Sandoz
From: Chloe Ross
Fax: 720-887-3910
Date: 5/22/06
Phone:
Pages: (including cover) 2
Re: Drop Ship
cc:

☐ Urgent ☒ For Review ☐ Please Comment ☒ Please Reply ☐ Please Recycle

·Comments:
Attn: Michelle

* Please fax or email confirmation of order: *

Attn Chloe' @ 800-599-9893

Thank you

McKesson Drop Ship Purchase Order

PO#? Page: 1 OF 1

Vendor: 0000017529
SANDOZ (FORMER GENEVA)
506 CARNEGIE CTR STE 400
PRINCETON NJ 08540
Vendor DEA:RG0165565

Customer PO No	RX23408M4262
PO Date	05/22/2006
Mck ref no	3001236071
Mck Acc #	
Buyer No	800-765-0595
Buyer	Chloe Ross
DC	ATLANTA DC#8148

Bill To:
MCKESSON DRUG COMPANY
P.O. BOX 819067
DALLAS, TX 75381-9067
MCK DEA: PR0040357

Ship To: 911609
PROVIDENCE HOSP PHCY-MOB
ASCENSION HEALTH
6801 AIRPORT BLVD HOS PHY
MOBILE AL 36608
DEA: AP0468656

Sold To: 911609
PROVIDENCE HOSP PHCY-MOB
ASCENSION HEALTH
6801 AIRPORT BOULEVARD
MOBILE AL 36608
DEA: AP0468656

Terms: 2.00% 64 Day(s) FOB: DESTINATION

****

Shipping: overnight 5/23/06
Contact: rebecca
Phone # 251-633-1352
REF# 3973083
DELIVER TO PHARMACY

****

Line# Description Economost#	Unit Price	Order Unit	Quantity	NDC/UPC# Net value
00003 643-50 NYDRAZID VL 100MG 10ML* 1461938	224.10	Each	6.000	NDC-00003 0643 50 1,344.60

TOTAL USD 1,344.60

Customer okayed short dating of 6/06. Also needs to have this for overnight 5/23/06. Thanks. Any ?'s plase contact Chloe @ 800-599-9894 X 5013.

The contract resulting from the issuance of this Purchase Order and acceptance thereof by you for products you distribute through us pursuant to this Purchase Order shall be subject to the terms and conditions set forth in the McKesson Buying Terms Form and any other supplemental terms communicated by McKesson to you in writing prior to the date of this Purchase Order. Any other terms and conditions proposed by you will not be applicable unless expressly approved in writing by McKesson.

Besse Medical
AmerisourceBergen Specialty Group

Facsimile Cover Sheet

To:	KIM
Company:	SANOZ
Phone:	609-627-8164
Fax:	720-887-3910
From:	Terry G. terry.gittinger@besse.com
Company:	Besse Medical Supply 9075 Centre Pointe Drive, Ste. 140 West Chester, OH 45069
Phone:	513-682-3649 or 800-543-2111 ext. 3049
Fax:	513-682-3629
Date:	5/22/06 Time:
Pages including this cover page:	2

COMMENTS:

PLEASE CONFIRM

Purchase Order

Besse Medical
AmerisourceBergen Specialty Group

Supplier: SANDOZ
2599 WEST MIDWAY BLVD
BROOMFIELD, CO
80020
800-525-8747

Deliver To: ASD/Besse Louisville Whse
345 International Blvd, #400
Brooks, Kentucky 40109

Purchase Order	Supplier ID	Reference	Date	DEA Number	Payment Terms
200022631	990000089	Acct 102042	05 22 2006	RA0219798	2% 60 Days Net 61

Above Purchase Order Must Appear On Invoice, Packing Slip, Bill of Lading and All Cases

Pos	Quantity Ordered	Unit	Product Code	Item # Description	NDC/UPC Number	Price	Extended Price
1	162	Ea	1055-60	24689 ARISTOSPAN 20MG/ML VL 5ML	51641-1056-00	26.00	4,212.00
2	5	Pk	3125-95	24797 NAFCILLIN SOD INJ 2GM VL 10/PK	00781 3125-95	134.02	670.10
3	71	Pk	3157-96	25964 CEFAZOLIN 1 GM VL 25X10ML	00781-3157-96	129.14	9,168.94
4	6	ct25	3157-70	26047 CEFAZOLIN 1GM VIAL EA	00781-3157-70	129.14	774.84
5	66	Ea	3210-46	26434 CEFTRIAXONE 10GM VL EACH SDZ	00781-3210-46	76.52	5,050.32
6	10	Pk	3407 95	27339 AMPICILLIN 500MG VL 10/PK	00781-3407-95	35.24	352.40
7	12	Pk	3408-95	27343 AMPICILLIN 2GM VL 10/PK	00781-3408 95	134.02	1,608.24
8	1	ct10	3408-95	27344 AMPICILLIN 2GM VL EA	00781-3408-95	134.02	134.02

Note: Backorder all shorts for 6 Months

Total Amount	21,970.86

Shipments invoiced after the 25th of the Month will be considered the 1st of the Month for discount purposes. Invoices for this shipment will be approved for payment only after receipt of the Merchandise.

Mail Invoices In Duplicate To: Besse Medical
9075 Centre Pointe Dr
Ste. 140
West Chester, OH 45069
Attn: Purchasing

TERRY

Buyer: Terry Gittinger /
terry.gittinger@besse.com
Phone: 513-682-3649
Fax: 513-682-3629

073341

PAGE 1/4

EON LABS MANUFACTURING, INC.
LOCK BOX 4108
CHURCH STREET STATION
NY NY

10261

DROGUERIA BETANCES, INC
CARR. #1 KM 34.0
REPARTO IND. CARTAGENA
CAGUAS, P.R. 00725 00000

5/22/06 EONLAB

BETANCES SHIPPER

JOSE VERDEJO José M. Verdejo

7 19352	12 FCO #BISOPROLOL FUMARATE 5MG X 100 00185077101		88.440	1,061.280
9 19354	12 FCO #BISOPROLOL FUMARATE 10MG X 100 00185077401		88.440	1,061.280
11 20057	72 FCO #BISOPROLOL HCTZ 5/6.25MG 100 00185070401		20.550	1,479.600
13 20191	24 FCO #BISOPROLOL HCTZ 10/6.25MG 100 00185070701		20.550	493.200
15 19931	24 FCO #BISOPROLOL HCTZ 2.5/6.25MG 100 00185070101		20.550	493.200
17 19949	12 CJA #CHOLESTYRAM LIGHT ORANGE CAJA 00185093998		57.020	684.240
19 19948	12 FCO #CHOLESTYRAM LIGHT ORANGE LATA 00185093997		28.510	342.120
21 20461	12 FCO #CHOLESTYRAM O/SUSP LATA ORANGE 00185094097		28.510	342.120
23 20044	48 CJA #CHOLESTYRAM O/SUSP SOBRE ORANG 00185094098		57.020	2,736.960

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PAGE 2

EON LABS MANUFACTURING, INC.
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5/22/06 EONLAB

BETANCES SHIPPER

JOSE VERDEJO

25 32530	12 FCO #FLUVOXAMINE MAL TAB 100MG 100 00185015701		198.110	2,377.320
27 13083	48 FCO #HYDROXYZ PAM CAPS 25MG X 500 30185061305		28.240	1,355.520
29 2863	48 FCO #HYDROXYZ PAM CAPS 50MG X 500 30185061505		36.070	1,731.360
31 15055	48 FCO #INDOMETHACIN E/R CAP 75MG 60 30185072060		92.170	4,424.160
33 15098	96 FCO #INDOMETHACIN E/R CAP 75MG 100 30185072001		153.620	14,747.520
35 24894	24 FCO #ITRACONAZOLE CAPS 100MG X 30 00185055030		231.010	5,544.240
37 19142	72 FCO #LABETALOL HCL TABS 200MG X 100 00185011701		35.000	2,520.000
39 20570	48 FCO #LABETALOL HCL TABS 300MG X 100 00018511801		46.000	2,208.000
41 19946	48 FCO #METHIMAZOLE TABS 5MG X 100 00185020501		27.930	1,340.640

073341

PAGE 3/4

EON LABS MANUFACTURING, INC.
LOCK BOX 4108
CHURCH STREET STATION
NY NY
10261

DROGUERIA BETANCES, INC
CARR. #1 KM 34.0
REPARTO IND. CARTAGENA
CAGUAS, P.R. 00725 00000

5/22/06 EONLAB

BETANCES SHIPPER

JOSE VERDEJO José M. Verdejo

43 19937	60 FCO #METHIMAZOLE TABS 10MG X 100 00185021001	48.250	2,895.000
45 21629	24 FCO #NABUMETONE TABS 500MG X 500 00185014505	481.510	11,556.240
47 21630	240 FCO #NABUMETONE TABS 750MG X 100 00185014601	113.730	27,295.200
49 21631	48 FCO #NABUMETONE TABS 750MG X 500 00185014605	568.640	27,294.720
51 15056	12 FCO #NITROGLYCERIN CAPS 2.5MG 100 00185517401	9.600	115.200
53 15057	12 FCO #NITROGLYCERIN CAPS 6.5MG 100 30185123501	10.650	127.800
55 23690	48 FCO #PHENDIMET TAR TABS 35MG X 100 00185405701	13.680	656.640
57 23895	48 FCO #PHENDIMETRAZ CAPS 105MG X 100 00185525401	60.000	2,880.000
59 12273	12 FCO #RIFAMPIN CAPS 300MG X 30 30185079930	42.770	513.240

073341

PAGE 4

4

EON LABS MANUFACTURING, INC.
LOCK BOX 4108
CHURCH STREET STATION
NY NY

10261

DROGUERIA BETANCES, INC
CARR. #1 KM 34.0
REPARTO IND. CARTAGENA
CAGUAS, P.R. 00725

00000

5/22/06 EONLAB

BETANCES SHIPPER

JOSE VERDEJO Jose M. Verdejo

61 19941	12 FCO #RIFAMPIN CAPS 300MG X 100 00185079901	142.560	1,710.720
63 15759	12 FCO #SOTALOL HCL TABS 80MG X 100 30185017101	28.120	337.440

120,324.96

PURCHASE ORDER

DATE: 05/22/06
PAGE: 1

VENDOR COPY

*** ORIGINAL ***

ORDER NUMBER: SPW08961
DATE ISSUED: 05/22/2006
TERMS:
SHIP VIA:
FOB:

VENDOR INFO
SANDOZ SERVICES, INC
C/O SANDOZ
P O BOX 840773
DALLAS, TX 75284
ATTN: LOUIS

SHIPTO INFO
HRS LLC (Wholesale Distribution)
WHOLESALE DIVISION 4965 South Avenue
~~3131 SOUTH BYRNE ROAD~~
TOLEDO, OH 43615
ATTN: Kathy Burkin

LN#	ORD QTY	HHS ITEM#	UofM	ITEM DESCRIPTION	UNIT PRICE	VALUE	NEEDED
1	96	00781153501	btlc	PSEUDOPHEDRINE 60MG TAB VENDOR PART# 00781153501	5.050000	484.80	05/29/2006
2	288	02144-0301c	btlc	PSEUDOPHEDRINE 30MG TAB VENDOR PART# 00781153301	3.400000	979.20	05/29/2006
						1,464.00	

Cheryl Rose 5-22-06
Approved By HHS/HRS CFO (or designated authority)